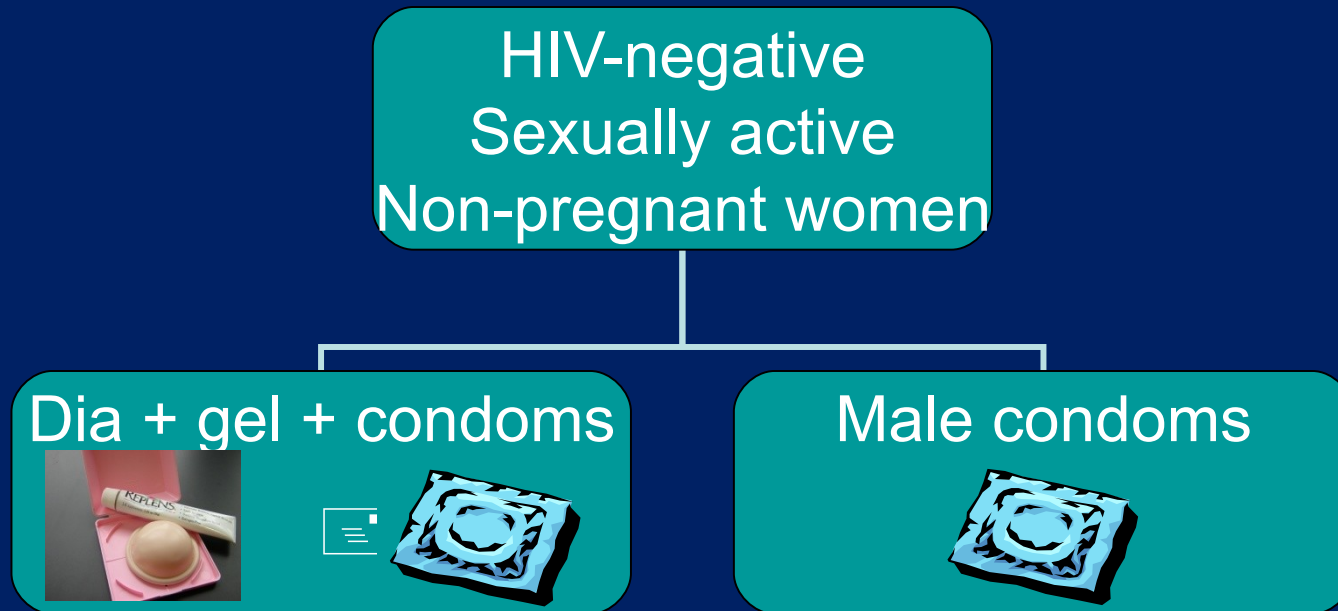


Deconstructing MIRA

Outline

- Review design and results
- What we could not assess
- Outstanding questions
 - Could adherence have been better ?
 - Should we consider alternative study designs?
 - Measuring self-reported behavior

MIRA Trial: Open label RCT



- All women received risk reduction counseling, free male condoms, diagnosis and treatment of curable STI
- Women were followed quarterly for 12-24 months, depending on time of enrolment

Trial Objectives

- Primary
 - **HIV incidence**
- Secondary
 - *Chlamydia trachomatis* (CT)
 - *Neisseria gonorrhoeae* (NG)

MIRA Trial Sites



UZ-UCSF
Harare, Zimbabwe
n=2502

PHRU
Soweto, South Africa
n=1028

MRC
Durban, South Africa
n=1515

Key Eligibility Criteria

- 18 – 49 years
- Sexually active
- Not pregnant
- HIV seronegative
- Able to correctly insert/remove diaphragm
- GC/CT negative or completed treatment of baseline GC/ CT infections

Results from ITT (intention-to-treat, results according to random assignment) (n=4948)

HIV	Incidence rate	Relative Hazard (95% CI)
All Sites	4.0	1.05 (0.84 – 1.32)
Harare	2.7	1.20 (0.83 – 1.74)
Durban	6.8	0.95 (0.69 – 1.31)
Johannesburg	3.4	1.05 (0.60 – 1.87)

Product Adherence (self-reported)

- In intervention arm:
 - Mean diaphragm use at last sex 73%
 - Mean % women ALWAYS using diaphragm since last visit: 58%
- Mean condom use at last sex
 - Intervention arm: 52%
 - Control arm: 85%
- HOWEVER, decreased condom use in the diaphragm arm did *not* translate into increased infection

Per-protocol Results

- Relative hazard of HIV incidence:
 - 0.90 (95% CI: 0.68 - 1.17) (use at last sex)
 - 0.83 (95% CI: 0.61 – 1.14) (use all the time since last visit)

Summary of primary result

- In the context of a comprehensive HIV prevention package offered to all participants, the trial found ***no additional protective benefit*** against HIV infection from providing the diaphragm plus lubricant in the intervention arm

MIRA Chlamydia Results

		No. of events	Proportion of pts with CT during follow-up (%)	Relative hazard (95 % CI)	p-value
ITT	Control	224	9.03	---	---
	Intervention	247	9.93	1.11 (0.93, 1.33)	0.25
Diaphragm used at last sex	Control	177	7.41	---	---
	Intervention	130	6.01	0.90 (0.72, 1.13)	0.35
Diaphragm always used in past three months	Control	201	8.23	---	---
	Intervention	110	5.62	0.84 (0.67, 1.06)	0.15

MIRA Gonorrhoea Results

		No. of events	Proportion of ppts with GC during follow-up (%)	Relative hazard (95 % CI)	p-value
ITT	Control	97	3.91	---	---
	Intervention	95	3.82	0.98 (0.74, 1.30)	0.90
Diaphragm used at last sex	Control	86	3.57	---	---
	Intervention	52	2.37	0.74 (0.52, 1.04)	0.09
Diaphragm always used in past three months	Control	89	3.63	---	---
	Intervention	35	1.77	0.61 (0.41, 0.91)	0.02

What MIRA could not assess...

- Whether new cervical barriers might work better
 - Coitally independent
 - Infrequent insertion
- Whether a diaphragm is as good as a condom
 - Whether, like condoms, diaphragms are effective if used consistently and correctly 100% of the time
- Whether a diaphragm is better than nothing

What MIRA could not assess: combination(multi-purpose) methods...

- Whether a barrier would be more effective with a microbicide or *vice versa*
- Utility for fertility control with (e.g. bufferGel) in HIV high prevalence settings
 - Whether multi-purpose/dual-purpose use would increase adherence

Effect of adherence + differential condom use

Post-trial simulations, with levels of diaphragm and condom use equivalent to that observed in our study sample:

- 70% diaphragm use (in intervention arm)
- 50% condom use in the intervention arm
- 85% condom use in the control arm



Power to detect a 33% reduction in incidence is $< 25\%$.

Need additional behavioral research to increase adherence!

Consider alternative study designs (given open label design)

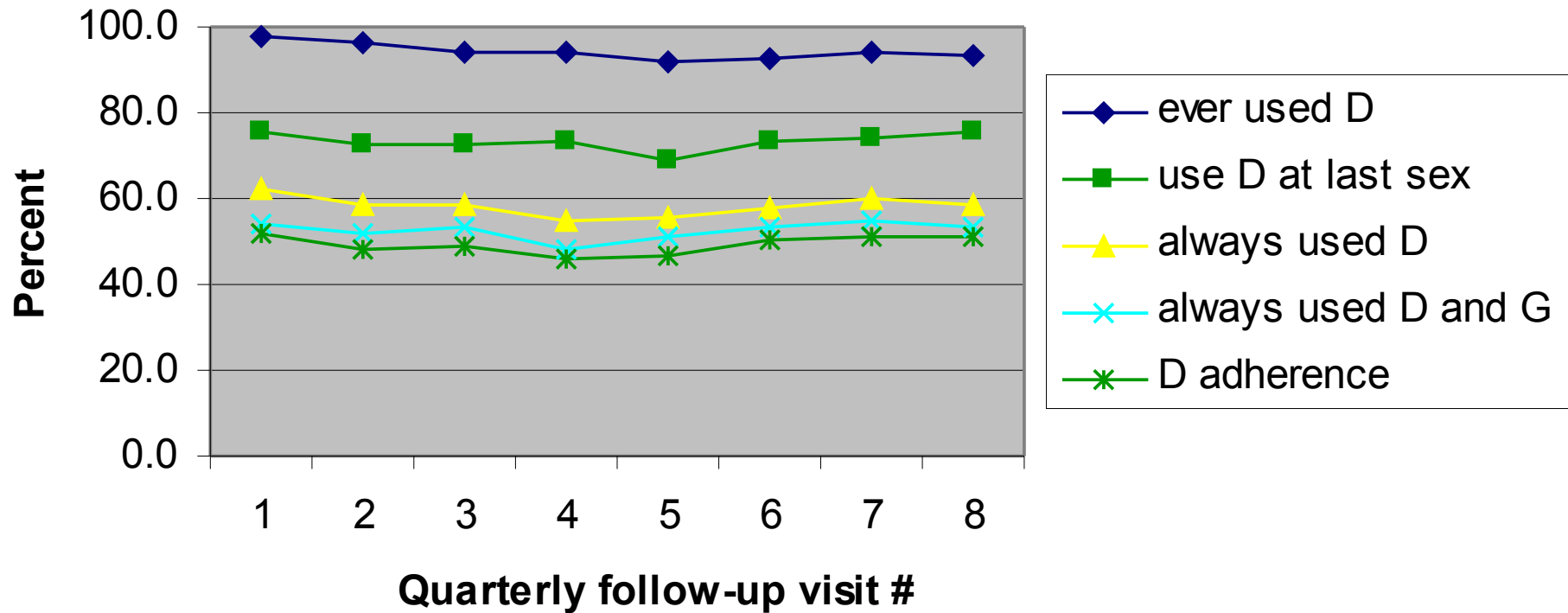
- Head-on comparison of intervention to condom (true equivalence)?
 - *Would require larger sample size, may provide “cleaner answer”, ethical issues*
- Condom “run-in”, or otherwise recruit women whose partners will not consistently use condoms
 - *(i.e. 2 phase study where no “condom migration” observed after introduction of diaphragms)*
- Adaptive designs (increase adherence)
 - Monitor adherence during the study even by study arm

Reconsider standards of condom counseling and other prevention methods during the trial (both arms) and beyond

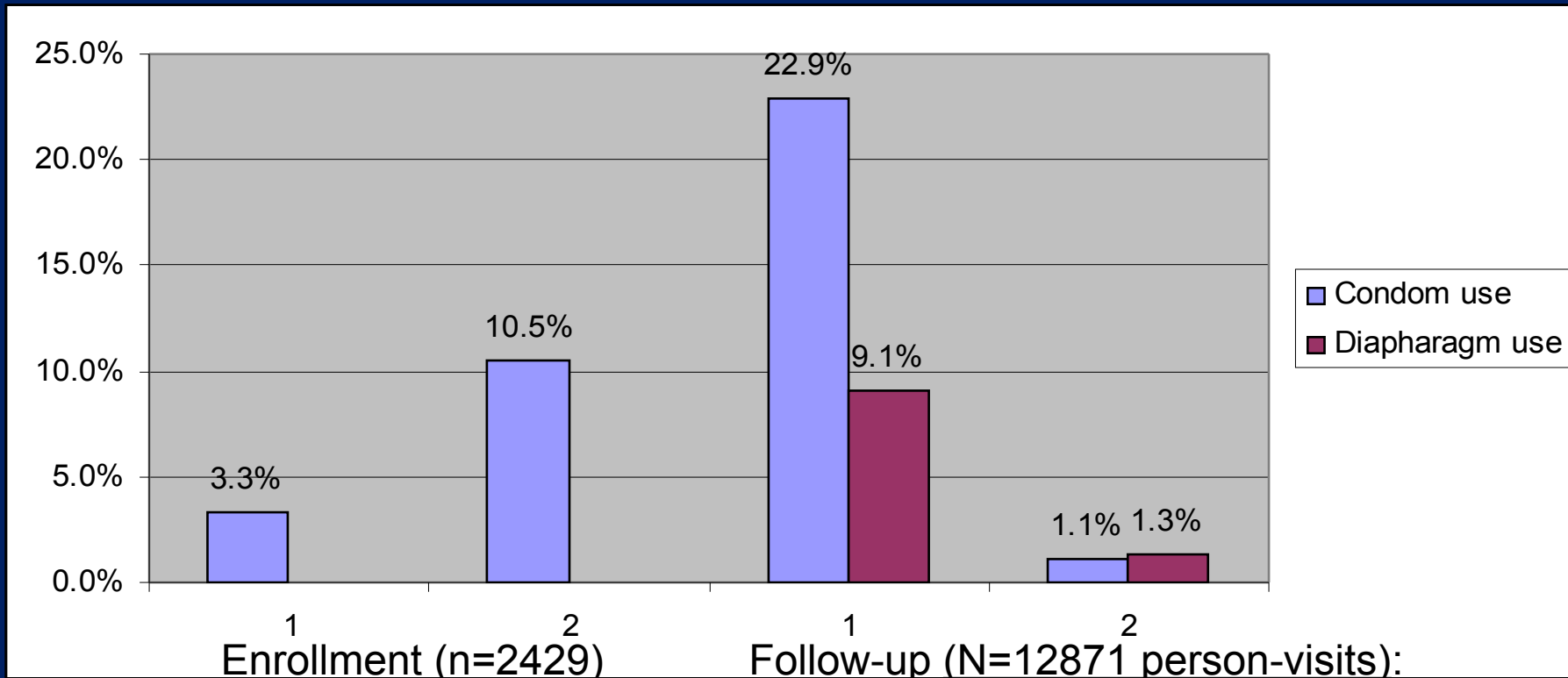
- More difficult to assess the intervention
 - Attenuation of power
- Community standard vs. enhanced counseling?
- Uncouple condom counseling from intervention protocols: e.g. as part of VCT prior to enrollment?
- Consider programs that sustain prevention programs in the community after the study

Measurement

Diaphragm and gel use by visit



MIRA: Discrepancies in ACASI reported product-use by time frame and visit



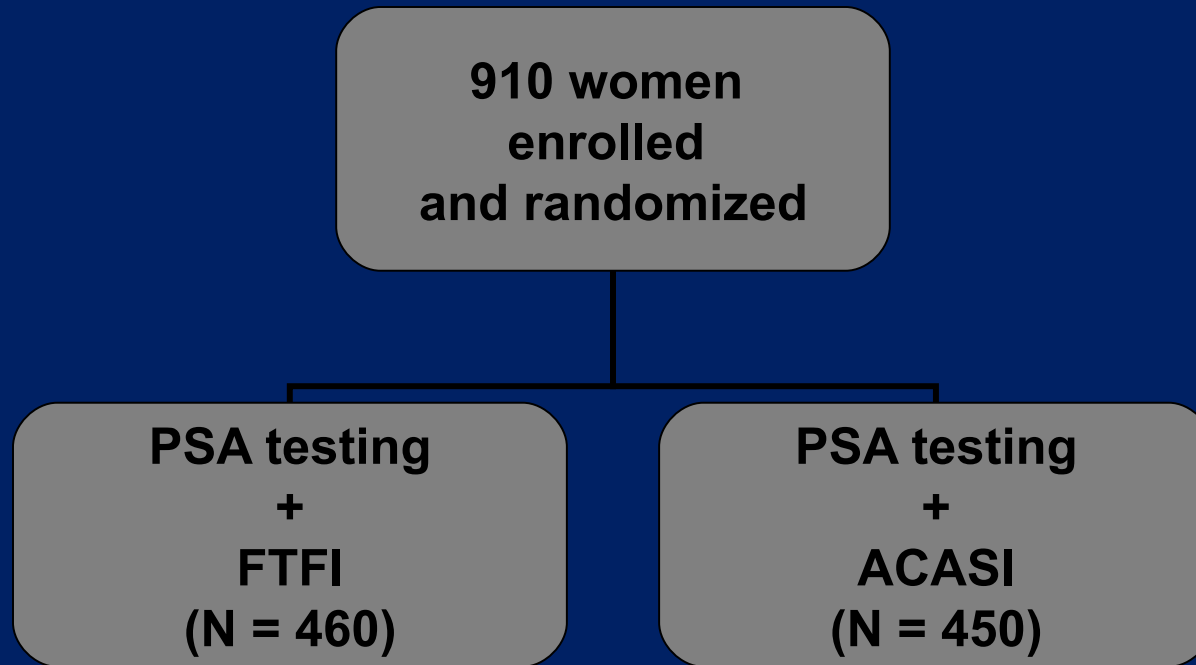
Comparison #1: those pts reporting that they *always* used product over the last 3 months, but reported *no* product use at last sex

Comparison #2 those pts reporting they *never* used product over the last 3 months, but reported that they *did* use a product at last sex

ACASI vs. Face-to-face interview

- Randomized, cross-sectional study of Zimbabwean women who had recently completed MIRA*
 - Objective 1: Measure the validity of self-reports of recent sex and condom use using an objective biomarker of semen exposure for the previous two days (i.e., prostate specific antigen (PSA)).
 - Objective 2: Evaluate whether ACASI improved the validity of self-reported data compared to standard face-to-face interviewing (FTFI).

ACASI vs. Face-to-face interview



- 196 participants (21.5%) had biological evidence of recent semen exposure (i.e. tested positive for PSA)
 - 104 participants in ACASI arm
 - 92 participants in FTFI arm

Results

N = 196 women who tested positive for PSA

Reported activity for past 2 days	Randomization group				P-value†
	ACASI (n=104)		FTFI (n=92)		
	No.	(%)	No.	(%)	
No sex	13	(12.5)	10	(10.9)	0.72
Only sex protected by a male or female condom	35	(33.7)	36	(39.1)	0.26

†Based on one-sided Fisher's exact test

Conclusions

- MIRA Results do not reject the hypothesis that coverage of the cervix could be protective
- Need behavioral research to increase *and* measure adherence
 - Self-reported behavior is unreliable. ACASI doesn't appear to significantly improve “honest” response
 - Need objective measures of product adherence to assess effectiveness and distinguish PRODUCT-related vs USER-Related issues
- New study designs needed to better evaluate interventions

MIRA Partners

- Research Triangle Institute International;
- University of California San Francisco
- Ibis Reproductive Health, USA & RSA
- University of Zimbabwe-UCSF Collaborative Research Programme in Women's Health, Zimbabwe
- Medical Research Council, RSA
- Perinatal HIV Research Unit, RSA
- Funder: Bill & Melinda Gates Foundation